

Jannis G. Stavrianopoulos et al.  
Serial No.: 08/486,070  
Filed: June 7, 1995  
Page 49 [Amendment Under 37 C.F.R. §1.116 (In Response To The  
October 10, 2001 Office Action -- April 10, 2002)]

**REMARKS**

Reconsideration of this application is respectfully requested.

Claims 718-1265 were previously pending in this application. Those claims have been canceled in favor of newly-added claims 1266-1575. Accordingly, claims 1266-1575 are presented for further examination on the merits.

Applicants and their attorney acknowledge with appreciation the indication in the October 10, 2001 Office Action that any rejections and/or objections not reiterated from the previous September 7, 2000 Office Action have been withdrawn.

**New Abstract and Title**

A new title and abstract of the invention have been submitted. The new title, "An Array of Substrates Having Surfaces for Nucleic Acid Analyses and Applications, and Composition of Matter Comprising a Plurality of Substrate Having Surfaces for Nucleic Acid Analyses and Applications," is believed to be more descriptive of Applicants' claimed invention herein. The new abstract (Exhibit 1) is also believed to be more descriptive of the present invention and in conformance with the Manual of Patent Examining Procedure (MPEP) §608.01(b) [Guidelines For The Preparation Of Patent Abstracts, pages 600-51 and 600-52]. This new abstract (Exhibit 1) should help future readers to ascertain quickly the character of Applicants' subject matter covered by their disclosure, including that which is new in the art to which the present invention pertains.

Entry of the new title and abstract is respectfully requested.

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### New Claims

In a sincere effort to claim subject matter commensurate with their original disclosure, Applicants have added new claims 1266-1562 above. These new are described in further detail below. In yet another sincere effort, this time to advance prosecution of this application by reducing or simplifying the issues for possible appeal, Applicants have canceled previously pending claims 718-1265, and in particular claims 873-1110. The latter claims were the subject of two separate prior art rejections for anticipation (35 U.S.C. §102(b)) and their subject matter is now longer being pursued.

As indicated above, new claims 1266-1562 have been added above in place of former and now canceled claims 718-1265. Claims 1266-1346 are directed to an array comprising a substrate having surfaces, each surface comprising at least one double-stranded nucleic acid fixed or immobilized thereto. As set forth in independent claims 1266, "at least one nucleic acid strand or a sequence therefrom comprises one or more non-radioactive chemical labels which comprise a non-radioactive signaling moiety or moieties which are quantifiable or detectable." Furthermore, according to claim 1266, "at least one nucleic acid strand or a sequence therefrom in one of said surfaces is different from at least one other nucleic acid strand or a sequence therefrom in another surface, and wherein said surfaces comprise siliceous matter or polymeric material." Claims 1267-1346 are directed to various embodiments of Applicants' claimed array including the nature of the siliceous matter (claims 1267-1269);<sup>1</sup> polymeric material (claims 1270-1275); surface treatment (claims 1276-1280); fixation or immobilization (claims 1281-1283); nucleic acid (claims 1284-1289); non-radioactive chemical label(s) (claims 1290-1311); quantifiable or detectable non-radioactive signal (claims 1312-

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<sup>1</sup> With respect to several dependent Markush claims (1268, 1273, 1349, 1354, 1432, 1437, 1507 and 1511, the element of "beads" has been included as a member. Support for this term is found in Applicants' specification, Example 1, page 15-16. The so-called "porous glass" treatment described by Weetal and Filbert ["Porous Glass for Affinity Chromatography Applications," Methods in Enzymology, Vol. XXXIV, Affinity Techniques Enzyme Purification: Part B, pages 59-72, Jacoby & Wilchek, editors] was actually carried out on glass beads.

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1331); signal detection (claims 1332-1335); nature of surface/surfaces (claim 1336); collection or sets of arrays (claims 1337-1340); and non-porous systems comprising arrays (claims 1341-1346).

Claims 1347-1424 are also directed to Applicants' array invention. As set forth in claim 1347, which is independent, Applicants claim an array "comprising a substrate having surfaces, each surface comprising at least one nucleic acid strand fixed or immobilized thereto, wherein at least one nucleic acid strand or a sequence therefrom in one of said surfaces is different from at least one other nucleic acid strand or a sequence therefrom in another surface, and wherein said surfaces comprise siliceous matter or polymeric material." As in the case of dependent claims 1267-1346, the various dependent claims to claim 1347 are directed to embodiments such as the nature of the siliceous matter (claims 1348-1350); polymeric material (claims 1351-1356); surface treatment (claims 1357-1361); nucleic acid (claims 1362-1367); non-radioactive chemical label(s) (claims 1368-1389); quantifiable or detectable non-radioactive signal (claims 1390-1409); signal detection (claims 1410-1413); nature of surface/surfaces (claim 1414); collection or sets of arrays (claims 1415-1418); and non-porous systems comprising arrays (claims 1419-1424).

Claims 1425-1575 are directed to compositions of matter. Claims 1425-1504 and claims 1505-1575 cover different compositions. As set forth in claim 1425, Applicants' invention is directed to a composition of matter comprising a substrate having a plurality of surfaces, each surface comprising at least one double-stranded nucleic acid fixed or immobilized thereto. Claim 1425 goes on to recite that "at least one nucleic acid strand or a sequence therefrom comprises one or more non-radioactive chemical labels which comprise a non-radioactive signaling moiety or moieties which are quantifiable or detectable, wherein at least one nucleic acid strand or a sequence therefrom in one of said surfaces is different from at least one other nucleic acid strand or a sequence therefrom in another surface, and wherein said

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surfaces comprise siliceous matter or polymeric material." As in the case of the other dependent claims discussed above, claims 1426-1504 are directed to various embodiments, such as the nature of the siliceous matter, polymeric material, surface treatment, fixation or immobilization, nucleic acid, chemical label(s), signal and signal detection, surface(s), collection or sets of such compositions of matter, and non-porous systems containing any such compositions of matter.

In claim 1505, a composition of matter is defined as "comprising a non-porous substrate having a plurality of surfaces, each surface comprising at least one nucleic acid strand fixed or immobilized thereto, and wherein at least one nucleic acid strand or a sequence therefrom in one of said surfaces is different from at least one other nucleic acid strand or a sequence therefrom in another surface, and wherein said surfaces comprise siliceous matter or polymeric material." The dependent embodiments for claim 1505 largely follow any of those dependent embodiments discussed above.

Applicants would respectfully point out that in drafting new claims 1266-1575, considerable attention was paid to the new matter rejection in the October 10, 2001 Office Action. Of the half a dozen new matter issues, it is believed that at least five of them have been obviated by the presentation of the new claims.

Entry of the new claims is believed to be appropriate and necessary. First, the new claims are not believed to raise new issues which would require further consideration and/or search by the Examiner, nor is any issue of new matter believed to be raised by the entry of the new claims. Moreover, it is believed that the new claims will actually serve to place this application in better form for appeal by materially reducing or simplifying the issues for appeal. As discussed above, all of the prior art rejections and virtually all of the new matter issues have been rendered moot by the presentation of new claims 1266-1575. Finally, the new claims are not believed to present additional claims without cancelling at least a corresponding number of finally

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rejected claims.<sup>2</sup> As indicated above, claims 873-1110 have been canceled altogether and have not been replaced by any of the new claims 1266-1575.

Entry of the new claims is respectfully requested.

#### Rejections and Objections in the October 10, 2001 Office Action

Two issues<sup>3</sup> were raised in the October 10, 2001 Office Action and are being addressed in this paper:

1. New matter (35 U.S.C. §112, first paragraph); and
2. Anticipation (35 U.S.C. §102).

#### The Rejection Under 35 U.S.C. §112, First Paragraph

Claims 718-872, 903, 906, 973, 976, 977, and 1111-1265 stand rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in such a way as to reasonably convey to one skilled in the art that the inventor(s), at the time the application was filed, had possession of the claimed invention. In the October 10, 2001 Office Action (pages 3-8), the Examiner stated:

A thorough review of the instant application had previously revealed that several of the claims contain NEW MATTER which was not disclosed as filed and was summarized in the previous office action, mailed 9/7/00, and is reiterated and maintained here.

[1] In claims 718-872 and 1111-1265 generic arrays are claimed. These claimed arrays start with the broadest versions in claims 718 and 1111 as only requiring a substrate surface with double-stranded nucleic acid fixed or immobilized thereto with at least one strand labeled as described in said claim. The closest array description, as filed, is given in the specification on page 16, lines 9-27. In this description the array also is limited to glass plates having depressions or wells with denatured

<sup>2</sup> Applicants and their attorney will leave the exact computation of the number of new claims to the discerning eye of the Patent Office's Patent Analyst.

<sup>3</sup> On page 12 in the October 10, 2001 Office Action, the Examiner objected to an informality in the disclosure (misspelling of the word "exoxy"). This informality has been corrected in the new claims presented above.

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analytes deposited therein, wherein single stranded analytes are fixed to the surfaces of the wells. Chemically labeled probes may then be hybridized to these analytes and subjected to detection of any probe-analyte hybrid. It is noted that the analytes are characterized as being "various" which supports the presence of "different" analytes deposited in each well or depression. It is additionally noted that plastic wells are a disclosed option as given in the bridging sentence between pages 20 and 21 of the instant specification. Polystyrene microfilter wells are described on page 22, lines 10-12, as a solid support. The practice of fixing polynucleotide analytes to conventional microtiter plates is described on page 23 at the start of Example 7. In summary, the array embodiments, as filed, are all at least directed to solid supports with wells or depressions therein. It is lastly noted that instant claims 718 and 1111 do not require either wells or depressions as being the form of the array of analyte fixation sites nor its being either glass or plastic, wherein microtiter arrays are deemed to be made of plastic. Such broader array embodiments which are NEW MATTER, for example, include flat surface arrays or non-glass or non-plastic arrays. Applicants have cited a multitude of passages from the instant application as filed but not one broadens the array practice to that which is claimed and indicated above as thus containing NEW MATTER. It is also noted that the Declaration of Dr. CHERYL H. AGRIS has been reviewed and supports the concept of a solid support with well etc. as has been noted before as having support as filed. However, nowhere in this Declaration has there been pointed to the broadening of array practice wherein "ONE" hybridization fluid or mixture simultaneously washes over all, or even a plurality, of the wells or depressions on such array surfaces. That is, whenever an array of wells etc. are described each well or depression etc. forms its own hybridization reaction mixture. Again, there is no array practice disclosed as filed for "ONE" hybridization fluid or mixture contacting, flowing over, or in any way simultaneously permitting overall array hybridization. Contrary to Declarant's allegations wishing to reduce the essential nature of this array practice broadening, the application, taken as a whole or in detail focuses cleanly on separate hybridization reaction mixtures wherever this level of detail is described and thus is essential regarding the scope of the disclosure of this issue.

[2] Several of the instant claims contain the limitation given as "glass-coated". This limitation is NEW MATTER in that glass-coated indicates a solid support which has a coating of glass over it. This coating type has not been found as filed. It is noted that coatings of various types are instantly disclosed such as coating of a solid support

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with a material which permits linkage, fixation, or immobilization of analytes, for example. Thus, the coating is not glass per se but rather optionally a linker coating on a glass solid support. The phrase "glass-coated" is indicative of a solid support having a glass coating thereon which is NEW MATTER in instant claims 724, 802, 875, 887, 958, 1029, 1041, 1117, and 1195. Applicants argue that a coating on a glass or plastic slide during an assay overcomes this rejection. This is non-persuasive because such a coating is limited to coating on glass or plastic and not the generic glass-coated or plastic-coated limitation which includes coating on glass or plastic as well as glass or plastic as a coating on another material.

**[3]** Several of the instant claims contain the limitation given as "plastic-coated". This limitation is NEW MATTER in that plastic-coated indicates a solid support which has a coating of plastic over it. This coating type has not been found as filed. Thus, similar to the above glass-coated NEW MATTER, the plastic-coated NEW MATTER is present in instant claims 727, 805, 878, 890, 961, 1032, 1044, 1120, and 1198. Applicants argue that a coating on a glass or plastic slide during an assay overcomes this rejection. This is non-persuasive because such a coating is limited to coating on glass or plastic and not the generic glass-coated or plastic-coated limitation which includes coating on glass or plastic as well as glass or plastic as a coating on another material.

**[4]** Several of the instant claims contain the limitation given as "oncogene" or combination thereof containing an oncogene. This limitation is NEW MATTER in that the limitation, oncogene, has not been found as filed. The amendment, filed 5/8/01, referred to the reference EP 63879 for support for these limitations. The next paragraph, below, explains why this is improper incorporation by reference and supports this rejection. The following claims contain this NEW MATTER: 743, 819, 906, 976, AND 1136.

**[5]** Several of the instant claims contain limitation directed to specific types of mutations given as deletion, inserted, inversion, point mutation, and a combination thereof. These limitations are NEW MATTER in that the limitations have not been found as filed. It is noted that the amendment, filed 5/8/01, indicated that these mutation types could be found in the publication EP 63879, cited on page 9 of the instant specification. Consideration of this page 9 citation reveals that it was cited as a reference which indicated mutations but no more detailed limitations. It was not cited for any other disclosure. This is an incorporation by reference of pointed to subject matter but not other

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subject matter. Such incorporations by reference must be directed to particular disclosures for them to be usable for giving written basis for claim limitations. A specific claim limitation is clearly essential subject matter. It is improper to [incorporate] by reference essential subject matter cited in a foreign patent application. It is improper to generically cite such a reference and then utilize it for anything therein without defining in the citation what it is cited for. In this case the publication was cited for non-radioactive signalling etc. review and not for mutation types. Thus, it does not serve as a proper basis for incorporating mutation types into the instant claims. For further discussion, see the M.P.E.P. at section 608.01(p), part I, subsection A. The following claims contain this NEW MATTER: 744, 820, 907, 977, and 1137.

**[6]** Several of the instant claims contain the limitation given as "partially double-stranded". This limitation is NEW MATTER in that the limitation has not been found as filed. In the amendment, filed 5/8/01, applicants indicate the "double-stranded" inherently gives written basis for this limitation. This is not deemed to be persuasive as double-stranded lacks any specificity such as partial character for this limitation. The following claims contain this NEW MATTER: 740, 816, 903, 973, and 1133.

The new matter rejection is respectfully traversed.

In order to ensure that each and every new matter issue has been addressed, Applicants' attorney has taken the liberty of inserting bold bracketed numbers before each issue in the rejection quoted above. The remarks below are directed to the designated numbers listed above.

**[1]** At the outset, Applicants would respectfully point out that prior to the advent of their present invention, solid phase nucleic acid detection formats were severely disadvantaged by slow hybridization rates which were largely the consequence of poor matrix capacity. The present invention overcame the problem of capacity in solid phase detection formats by uniquely enhancing the fixation or immobilization of nucleic acid strands to the surfaces of substrates.

The Patent Office has taken the position that Applicants' claimed array practice is limited to the inclusion of wells or depressions. This is not the case. Applicants'

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disclosure in no way limits their array practice to wells or depressions. As stated in earlier responses, the passage on page 16, lines 9-27 referenced in the Office Action begins with the introductory phrase "For example, . . ." A person of ordinary skill in the art would have understood that the description on page 16 (lines 9-27) to be illustrative and not a limitation on Applicants' claimed invention.

In Applicants' May 30, 2001 Communication, charts were transmitted to show that their array practice was applicable to any substrate or surface, regardless of shape or topology. In the chart submitted as Exhibit 4 to their May 30, 2001 Communication, Applicants highlighted support within their specification for the claimed genus "Array of Substrate Surfaces." This information does indeed show that Applicants are entitled to the full scope of their array practice as now claimed.

Before closing, Applicants would like to point out further that their specification provides numerous instances where fixation or immobilization of nucleic acids to the surfaces of substrates is carried out, such instances clearly not being limited to wells or depressions. On page 15, reference is made under "DETAILED DESCRIPTION" of "methods for fixing the analyte to a non-porous solid support, . . ." Later on the same page under "EXAMPLE 1," further reference is made to "an analyte is immobilized on a solid support." Neither passage limits fixation or immobilization to wells or depressions.

Further in the specification on page 20 under EXAMPLE 5, Applicants describe a probe that is "immobilized on a non-porous plastic surface" and that "the adherence or fixing of DNA to a polystyrene surface is improved . . ." Moreover, Applicants disclose:

Previous experiments demonstrated that addition of duodecadiamine (DDA) to polystyrene resulted in a uniform binding coefficient of polystyrene plates of different batches. Another technique for improving the fixing or uniformity of the plastic surface for fixing DNA involves the treatment of the surface with polylysine (PPL).

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Polystyrene plates are also commonly referred to as "Petri dishes" and unquestionably possess flat surfaces which are not wells or depressions.

Again, on pages 21-22 (EXAMPLE 6) in the specification, Applicants disclose labelled, non-biotinylated denatured DNA [2000 ng to 5 ng] [being] "applied to the same DDA-coated polystyrene plates referenced on page 20 in the specification.

Lastly, on page 23, when Applicants describe "treatment of glass or polystyrene surfaces" at the top of the page, they are referring to surfaces -- but not surfaces with wells or depressions. In lines 4-5 on page 23, Applicants specifically describe:

These epoxy solutions are applied to the surfaces or wells, . . .

This last phrase clearly shows that surfaces or wells connotes different elements, but elements which can both be usefully employed in accordance with Applicants' present invention.

Reconsideration and withdrawal of the first ground of new matter rejection is respectfully requested.

**[2]** The term "glass-coated" is not recited in any of the new claims. Thus, this ground of rejection has been rendered moot.

**[3]** Likewise, the term "plastic-coated" is not to be found in any of the new claims. This ground has also been rendered moot by the new claims.

**[4]** The term "oncogene" does not appear in any of the new claims. Thus, this ground of rejection is no longer applicable.

**[5]** The specific types of mutations are not recited in the new claims. This ground of rejection has also been rendered inapplicable.

**[6]** The term "partially double-stranded" is not recited in any of the new claims. This ground should no longer apply, therefore.

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**The First Rejection Under 35 U.S.C. §102**

Claims 873, 874, 878-880, 882, 883, 886, 890-892, 894, 901, 903-906, 908-917, 924-957, 961-963, 971, 973-976, 978-987, 994-1028, 1032-1034, 1036, 1040, 1044-1046, 1048, 1055, 1057-1060, 1062-1071, and 1078-1110 stand rejected under 35 U.S.C. §102(b) as being clearly anticipated by Kourilsky et al., United Kingdom (UK) 2,019,408. In the Office Action (pages 9-10), the Examiner stated:

This rejection is reiterated as necessitated by amendment regarding newly added claims. Applicants argue that photometric means is now in the claims and not in the reference. In response the enzymatic detection of the reference generates a colored dye reaction which is clearly photometrically detected. As previously described of record Kourilsky et al. discloses the centrifugal fixation of a target/probe hybrid with a chemical label thereon on page 3, lines 18-54, with evaluation of bound probe via a  $\beta$ -galactosidase in solution of the resuspended hybrids. The quantitation limitations in instant claims are a capability which clearly is present considering the solution enzyme determination of Kourilsky et al. and thus is anticipated by the reference, even though Kourilsky et al. does not perform the quantitation while the hybrids are still fixed on the support. Also, centrifuge tubes for such a centrifugal procedure are well known to be made of translucent, non-porous, plastic. Several added instant limitations directed to various bridging moieties and immobilization via hybridization of the probe are deemed anticipated by the somewhat complex assemblage of the probe/target hybrid and label moieties in that portions are direct, portions are indirect, etc. The probe is clearly immobilized via hybridization. Otherwise the assay would be non-functional if non-hybridized probe also was fixed by the centrifugation step.

In view of the above cancellation of the rejected claims at hand, the first anticipation rejection has been rendered moot and irrelevant. Withdrawal of the first rejection under 35 U.S.C. §102(b) is respectfully requested.

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**The Second Rejection Under 35 U.S.C. §102**

Claims 873, 874, 878-880, 882, 883, 886, 890-892, 894, 901, 903-906, 908-917, 924-957, 961-963, 971, 973-976, 978-987, 994-1028, 1032-1034, 1036, 1040, 1044-1046, 1048, 1055, 1057-1060, 1062-1071, and 1078-1110 stand rejected under 35 U.S.C. §102(b) as being clearly anticipated by . In the Office Action (pages 9-10), the Examiner stated:

This rejection is reiterated as necessitated by amendment. Again, applicants argue that photometric means is not in the reference and again this is non-persuasive as fluorescent detection is clearly a photometric means of detection. Stuart et al. discloses the practice of in-situ hybridization on a coverslip with fluorescent antibody detection of probe/target hybrids in column 6, lines 17-57, which anticipates the above instant claims. The target samples were prepared on acid washed microscope slides as indicated in column 4, lines 61-67. The slides and coverslips at the time were well known to be transparent glass and non-porous and form a system. The acid washing is deemed a surface treatment. The fluorescent labeling is deemed a type of chemical label because instant dependent claims includes fluorescent labeling in the signalling limitations. It is noted that Stuart et al. does not disclose quantitation of signal but it is also noted that the instant claims are directed to a capability for quantitation of label and are not method claims. A fluorescent label is utilized in Stuart et al. emits light which is well known to be quantifiable and thus anticipates the instant claims listed above. See the below paragraph which cites legal decisions as to shifting the burden to applicants to distinguish the reference disclosure over the invention when the claimed subject matter is expected to anticipate the claimed invention but not measured in a cited prior art reference. Ward et al. also cites in-situ hybridization with detection with avidin-peroxidase in columns 19-20 therein which reads on the above claims also due to the quantifiability of such signals.

It is noted that *In re Best* (195 USPQ 430) and *In re Fitzgerald* (205 USPQ 594) discuss the support of rejections wherein the prior art discloses subject matter which there is reason to believe inherently includes functions that are newly cited or is identical to a product instantly claimed. In such a situation the burden is shifted to the applicants to "prove that subject matter shown to be in the prior art does not possess characteristics relied on" (205 USPQ 594, second column, first full paragraph).

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The second anticipation rejection is respectfully traversed.

**Informality**

The misspelling of the word "expoxy" has been corrected in the new claims. In addition, the inadvertent misspelling of the word "substrate" (spelled "substratae") in former and now canceled claim 1265 has been corrected in the new claims.

Favorable action is respectfully requested.

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### SUMMARY AND CONCLUSIONS

Former claims 718-1265 have been canceled in favor of new claims 1266-1575 which are presented for further examination on the merits.

No claim fee for adding new claims 1265-1575, the number of new claims and independent claims being smaller than any previously paid for. As indicated in the accompanying Transmittal form, authorization is hereby given to charge any deficiencies to Deposit Account No. 05-1135. This Amendment is also accompanied by a Request For An Extension Of Time (3 months) and authorization for the large entity fee therefor. No other fee or fees are believed due in connection with this filing. In the event that any other fee or fees are due, however, The Patent and Trademark Office is hereby authorized to charge the amount of any such fee or fees to Deposit Account No. 05-1135, or to credit any overpayment thereto.

If a telephone conversation would further the prosecution of the present application, Applicants' undersigned attorney request that he be contacted at the number provided below.

Respectfully submitted,

  
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AN ARRAY COMPRISING A SUBSTRATE HAVING SURFACES FOR NUCLEIC ACID ANALYSES AND APPLICATIONS, AND COMPOSITION OF MATTER  
COMPRISING A PLURALITY OF SUBSTRATES HAVING SURFACES FOR  
NUCLEIC ACID ANALYSES AND APPLICATIONS

Abstract Of The Disclosure

Nucleic acid arrays are useful for nucleic acid analyses and a host of applications, including detection, mutational analysis, quantification and sequencing. Such arrays are designed and provided on solid supports by fixing or immobilizing nucleic acid strands to the surfaces of the substrate. Such fixed or immobilized nucleic acid strands may be hybridized to nucleic acid strands or sequences therefrom which have been labeled non-radioactively and are detectable non-radioactively. The labeled nucleic acid strand comprises one or more non-radioactive chemical label or labels which comprise a non-radioactive signaling moiety or moieties which are quantifiable or detectable. The nucleic acid arrays provided by this invention comprise different nucleic acid strands or sequences therefrom, i.e., at least one nucleic acid strand or sequence therefrom in one substrate surface is different from at least one other nucleic acid strand or sequence therefrom in another substrate surface. The substrates can be porous or non-porous, transparent or translucent, and they can be made from a great number of different materials, e.g., glass, plastic, and can assume a great number of shapes, e.g., plates, wells, depressions, tubes, cuvettes, and collections or sets of such plates, wells, e.g., microtiter wells, depressions, tubes or cuvettes. The surfaces can vary, and, along with the substrates, the surfaces can also be treated with surface treatment agents, including, for example, DDA, PPL,  $\gamma$ -aminopropyltriethoxysilane, ammonium acetate and epoxy compounds. Treatments can be made to glass or plastic surfaces.

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